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(54) Title: N-ACETYL GLUCOSAMINE AS GASTROPROTECTIVE AGENT

(57) Abstract

This invention relates to the novel use of N-acetyl glucosamine (NAG) to treat gastritis and to maintain the integrity and normal function of the upper gastrointestinal (GI) tract. A method of treating gastrointestinal mucous membrane disorder in the gastrointestinal tract of a human being comprising feeding the human being a therapeutic amount of N-acetyl glucosamine on a regular periodic basis.

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N-ACETYL GLUCOSAMINE AS GASTROPROTECTIVE AGENT

FIELD OF THE INVENTION

This invention relates to the novel use of N-acetyl glucosamine (NAG) to treat gastritis and to maintain the integrity and normal function of the upper gastrointestinal (GI) tract.

BACKGROUND OF THE INVENTION

Gastritis, which is an upper gastrointestinal (GI) tract complaint, is a very common condition affecting a substantial portion of the population. The treatment is symptomatic and self-medication with common over-the-counter substances, such as antacids (ROLAIDS and TUMS) and lining coatings (PEPTOBISMOL), together with prescribed medication procedures, represents an enormous annual expenditure.

While certain conditions of the upper GI tract are well-defined, many cases are milder in nature and may or may not be the forerunner of more serious conditions. The upper GI tract is the site of several sources of potential damage such as the hydrochloric acid of the stomach, the powerful detergent action of bile salts and the digestive enzymes from the pancreas, which enter through the common duct into the intestine a few centimeters below the stomach, into the duodenum.

Gastritis can include inflammation of the stomach lining. There are several established factors implicated, including excess secretion of stomach acid, infection with the microorganism Helicobacter (Campylobacter) pylori, reflux of bile and pancreatic secretions and severe restriction of blood flow to the stomach lining. Interruption of blood flow by intense vasoconstriction occurs in victims of severe trauma, such as burn victims, and can

result in breakdown of the protective lining of the stomach and duodenum and erosion leading to ulceration within hours.

In the past, most treatments have been directed at reducing acid secretion in the stomach. In recent years, agents have been used to increase the defensive structures. An important role is played by prostaglandins which are regulators of tissue function formed in all cells under certain conditions. These play a key role, for example, in initiating the inflammatory response of the lining. The anti-inflammatory effects of corticosteroids and of non-steroidal anti-inflammatory drugs (NSAID) are attributed in large measure to the inhibition of prostaglandin formation. This inhibition, however, also affects the action of these substances on many other processes, including the synthesis of many tissue components. This in turn is responsible for the undesired side-effects of these drugs, such as stomach and GI tract erosion and bleeding which are often severe and sometimes life-threatening (Harrison's Principles of Internal Medicine, 12th Ed., 1991, p. 1244 et seq.). This is attributed to breakdown of the protective lining.

A drug, Proglumide (trade-mark), which protects against gastric erosion and ulceration, was found to stimulate the incorporation of N-acetyl glucosamine into the glycoproteins etc. which form the protective coat of the GI tract. The benefits of the drug were attributed to this action (Umetsu et al., European Journal of Pharmacology 1980, 69:69-77).

Several patents disclose amino sugars for treatment of disorders.

U.S. Patent No. 4,590,067, May 20, 1986, Meisner, Peritain Ltd., discloses a composition for preventing and

treating periodontal disease comprising bone meal, ascorbic acid, tyrosine and either glucosamine or cysteine. N-acetyl glucosamine is not disclosed.

French Patent No. 2,473,887, July 24, 1981, discloses the use of biochemical precursors of glucosamine-glycans for the treatment of vascular disorders of functional or organic origin in which there is insufficient blood flow to the limbs, for asphyxic hypoxydotic symptoms, and in cosmetology, for skin defects caused by insufficient circulation to the skin. The precursors, which include N-acetylglucosamine, increase the elasticity of perivascular tissue, resulting in an increase in arterio-capillary blood flow, without causing a vasodilating action.

United States Patent No. 4,006,224, February 1, 1977, J.F. Prudden, discloses the treatment of ulcerative colitis or regional enteritis in a mammal by administering D-glucosamine, or one of its salts. Equal or superior results to the conventional treatments of the two conditions are claimed. The dose is 20-300 mg/kg of D-glucosamine, HCl daily. In a clinical trial, a patient with Crohn's Disease that was not affected by ACTH or prednisone was given D-glucosamine, HCl subcutaneously. The symptoms purportedly stopped after several weeks of treatment.

WO A 8 702 244, N. Hendry, EP A 0178602, Peritain Ltd. and French Patent A 2016 182, Rotta Research Labratorium SpA, are of interest.

Hendry discloses a preparation for tissue growth regulation comprising (a) at least one of N-acetyl-D-glucosamine or an oligomer thereof, or a deacylated derivative thereof, or a substituted product of these compounds; (b) at least one of biotin or an analog or derivative biotin, or biologically active residue thereof; and (c) a

divalent metal cation together with a pharmaceutically acceptable anion.

Both Meisner and Hendry above refer to amino sugars, including glucosamine and N-acetyl glucosamine. Their use is as one of a mixture of several other known nutrients, which have various claimed effects on cell growth.

An article entitled "Decreased Incorporation of ^{14}C-Glucosamine Relative to ^{3}H-N-Acetyl Glucosamine in the Intestinal Mucosa of Patients with Inflammatory Bowel Disease", A.F. Burton and F.H. Anderson, vol. 78, No. 1, 1983, American Journal of Gastroenterology, discloses evidence that the synthesis of glycoproteins in intestinal mucosa of patients afflicted with inflammatory bowel disease is deficient in the diseased tissues of such patients. The article discusses possible reasons for the deficiency. However, no suggestions for alleviating the deficiency are made.

SUMMARY OF THE INVENTION

The invention is directed to a method of treating gastrointestinal mucous membrane disorder in the upper gastrointestinal tract of a human being comprising feeding the human being a therapeutic amount of N-acetyl glucosamine on a regular periodic basis.

The N-acetyl glucosamine can be fed to the human being on a daily basis. The human being can be fed about 300 mg to about 10,000 mg of N-acetyl glucosamine per day, or about 1,000 mg to about 6,000 mg of N-acetyl glucosamine per day, or about 500 mg of N-acetyl glucosamine per day.

The N-acetyl glucosamine can be incorporated in a pharmaceutically acceptable carrier, and can be fed to

the human being only as required to restore the integrity of mucous membrane tissues in the gastrointestinal tract.

The invention is also directed to a composition useful for treating gastrointestinal mucous membrane disorder in the gastrointestinal tract of a human being comprising N-acetyl glucosamine and a pharmaceutically acceptable carrier. The N-acetyl glucosamine can be present in the amount of about 1,000 mg to about 6,000 mg or in the amount of about 500 mg.

The invention pertains to a method of inhibiting gastrointestinal mucous membrane disorder in a mammal caused by administration of pain alleviating agents which comprises feeding the mammal a therapeutic amount of N-acetyl glucosamine in combination with a therapeutic amount of a pain-relieving agent.

The pain relieving agent can be selected from the group consisting of acetaminophen and acetylsalicylic acid. The pain alleviating agent can be acetylsalicylic acid or acetaminophen.

The invention also pertains to a composition for alleviating pain and inhibiting gastrointestinal mucous membrane disorder in a human being which comprises a mixture of a therapeutic amount of N-acetyl glucoasmine and a therapeutic amount of a pain-alleviating agent.

The pain alleviating agent can be selected from the group consisting of acetaminophen and acetylsalicylic acid. The pain alleviating agent can be acetaminophen or acetylsalicylic acid.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The invention is directed to the use of N-acetyl glucosamine (NAG) as a source of amino sugar for the synthesis of molecules such as glycoproteins and glycosaminoglycans, which are rich in NAG. The synthesis of glycoproteins and glycosaminoglycans is stimulated by NAG.

In the body, NAG is formed from glucosamine. NAG is then directly converted into other amino sugars. NAG is a key substance in protein and tissue construction. The applicant has discovered that in intestinal tissue synthesis, the formation of NAG itself from glucosamine is a slow part of the overall process. If the presence of NAG is deficient, the whole tissue construction process is inhibited. This necessitates the use of NAG, specifically, and not a de-acetylated form, or oligomer.

NAG is a more stable substance than glucosamine, is a neutral substance and is readily assimilated and utilized by tissues whereas most oligomers are not.

The novel feature of the invention is the use of an external source of N-acetyl glucosamine (NAG) to promote the synthesis of the glycoproteins and glycosaminoglycans which form the protective barrier in the upper gastrointestinal tract. The synthesis of these substances is dependent upon an ample supply of NAG which, if available in the body, is utilized for these biosynthetic processes.

While there are several factors involved in any disease process, some more than others are responsible for the more serious aspects of the disease. Regardless of other factors, the maintenance of the protective upper gastrointestinal lining is vital. Other facets of the disease might or might not be affected, but rectifying the most important processes is essential. We have discovered

that providing an external ingested supply of NAG is a good physiological way of accomplishing this.

There are tissue defects in the digestive tract of human beings suffering food intolerance or food allergies. These defects can be corrected to enable the mucosa in the tract to form a necessary barrier to transmission of food allergens and to maintain normal function. The mucosa tissue structure is rich in amino sugars derived from N-acetyl glucosamine. We have discovered that the availability of N-acetyl glucosamine is critical to its synthesis.

We have also discovered that an external source of N-acetyl glucosamine is useful to ensure adequate synthesis of the mucosal barrier. Indeed, we have found that the use of N-acetyl glucosamine alone might be sufficient in itself to treat milder food allergy cases. In more severe cases, the amino sugar, N-acetyl glucosamine might be combined with elemental diets so that the removal of offending substances is accomplished, while at the same time, providing the new amino sugar material necessary to enable the human body to generate coherent mucosa tissue and maintain its defenses.

N-acetyl glucosamine (NAG) is an amino sugar which is formed in all animal cells and is utilized for the synthesis of many cellular components. The biochemical process by which these components are made is similar in all cells although the end products differ depending upon the type of cell involved. Most of the end products are found outside the cells where they form sheaths which bind cells together, and are major structural components, as in the walls of blood vessels, and fill the spaces between cells, i.e. the interstitium. Amino sugars are found combined with other large molecules (macromolecules) of protein, lipid (fats) or other carbohydrates to form

glycoproteins (GP), glycolipids (GL) and glycosaminoglycans (GAG). Glycoproteins have many functions, some circulate in the blood, others are anchored on the surface of cells, as are glycolipids. They can confer unique properties to the cell, for example, on the surface of red blood corpuscles there is a glycolipid which determines the blood groups A, B and O. The sole difference between these groups is the presence of a single amino sugar. Such remarkable specificity indicates that there is a "language" in which amino sugars are the "letters" analogous to the genetic code, by which biological information is recorded and put into action.

Each cell makes its own amino sugars and the process, as in the case of most biochemical synthesis, is regulated by the availability of the first member of the sequence, which in this case is glucosamine. Glucosamine is formed in the body from the pool of sugars derived from glucose, blood sugar, and is acetylated to form N-acetyl glucosamine (NAG). NAG is the immediate precursor for two other amino sugars, N-acetyl galactosamine and N-acetyl neuraminic (sialic) acid. These amino sugars constitute about half the total weight of the GAG found in human tissues (References 1-7).

In the synthesis of these molecules, the availability of the substrate, amino sugars, is critical to proper function. We have discovered that although the formation and utilization of amino sugars takes place in all human cells independently, an external source of amino sugar is readily taken up by the cells and is utilized by them for incorporation into the macromolecules. An external source of amino sugar, we have found, can provide for an adequate amount of substrate to satisfy cell demands which otherwise might be greater than the cells can meet.

The interstitium is the space between the cells which contains the fibrous protein collagen ensheathed by glycosaminoglycan (GAG). The GAG absorbs very large quantities of water to form a gel-like material which resists compression thereby giving shape and firmness to the tissue. This material acts as a medium which regulates the passage of nutrients, etc., between the blood and the tissues, and also acts as a barrier, for example, to the spread of infection (Bert and Pearce).

Mucous membranes are covered by a microscopically thin glycoprotein rich in sialic acid called the glycocalyx. In the upper gastrointestinal tract (GI), this microscopically thin layer is the ultimate barrier between the underlying tissue and corrosive digestive juices in the tract. When the layer is damaged, erosion and ulceration of the underlying tissue occurs. If the blood supply to the upper GI is arrested for about 5 minutes, for example, it has been found that all synthetic processes cease, including formation of the glycocalyx, and an ulcer can be seen forming within an hour. This illustrates the dynamic nature of the biological processes in the human body. There are several hundred grams of amino sugar in the various tissue components of the body but the average life of a given molecule is only 3 days or so. There is thus a constant turnover of all molecules in the body, even in tissues such as bone, and a constant supply of substrates for synthesis is therefore required.

An important and novel feature of the present invention is the discovery that increased demands caused by injury such as food allergen injury can be placed upon cells which might strain their resources, and in this situation, an external supply of amino sugars is beneficial. In the gastrointestinal tract (GI), the rate of synthesis of the glycocalyx had been considered to be adequate in persons afflicted with Inflammatory Bowel

Disease (IBD). However, in these persons, as in many situations where there is disease or injury, we have found that the turnover of cells is increased, perhaps as much as threefold. This creates a demand that is beyond what is considered normal. We have found that the rate of incorporation of NAG into the intestinal mucosal tissue of the upper GI tract is three times greater in persons afflicted with gastritis than in those who are not afflicted.

We have also found that in human placenta near term, the formation of glycosaminoglycan (GAG) is stimulated strongly by the steroid 17 α-hydroxyprogesterone (Burton et al.) which appears to function by increasing the synthesis of amino sugars. We have discovered that the same stimulation can be achieved merely by providing the appropriate amino sugars.

Others have shown that in chondrocytes, the cells which form cartilage, the presence of corticosteroids inhibits the formation of GAG. Supplying amino sugars largely overcame this inhibition (Fassbender).

In a recent publication, the question of intestinal permeability in persons with Crohn's Disease, a form of IBD, was reviewed (Olaison et al.). It was found that these persons have greater than normal permeability of the GI tract which leads to the absorption into the bloodstream of substances normally excluded. This includes the substances which cause food sensitivities or food allergies. The condition is attributed to a defect in the mucosal barrier, the glycocalyx, and the intercellular cement composed of GG. Even unaffected relatives of these patients have been found to have increased permeability (Hollander et al.) which supports the concept that some individuals have a genetic or constitutional defect which sets the stage for a spectrum of disorders ranging from

mild to serious food intolerance to severe inflammatory lesions.

Various agents inhibit the formation of the mucosal barrier including ethanol, aspirin and other anti-inflammatory agents. Erosion and bleeding of the GI tract is a major side-effect of such drugs.

Inflammation is a common accompaniment of many forms of injury and is part of the body's defence and repair mechanism. Often, however, the inciting agent is such that the inflammation serves no protective purpose and in fact results in tissue damage causing pain and disability, as in arthritis.

There are, therefore, many situations where an external source of amino sugar can be beneficial. We have found that a good choice is N-acetyl glucosamine (NAG) which is a neutral compound, is stable, is very soluble, is tasteless, and is readily absorbed from the digestive tract. It circulates in the blood with a half-life of about 4 hours. Very little is excreted since it is a "committed metabolite" utilized exclusively for the synthesis of GP, GL, GAG in tissue components. We have found that when an external supply of NAG is fed to a patient, it is readily taken up and utilized by the human body. It therefore has the potential to be of benefit in many situations where the synthetic processes are less than adequate to meet demands. NAG alone is capable of efficient utilization for these processes when taken by mouth.

Example 1

Case History - T.L.

T.L., male, age 23, began suffering sharp abdominal pain in 1985, and a general intolerance of foods except for rice and a few other things. He could not tolerate

fibre, fried foods, etc. He was prescribed an anti-ulcer regime which caused little improvement. In 1987, he was given cimetidine and sulcrate, anti-ulcer agents. Colonoscopy and gastroduodenoscopy in 1987-88 were negative. He was also diagnosed as asthmatic, and allergic to grass, dust, trees, hair and some foods.

T.L. began ingesting NAG at a rate of 3 g per day in October, 1988. His symptoms improved in three weeks. He continued NAG treatment and reported that at eight months, his symptoms had all been alleviated, including the asthma. He continues to have some sensitivity to caffiene and alcohol, which he avoids, but he can now eat a wide variety of foods including salads and high-fibre items, without difficulty. T.L. no longer suffers nausea and "heaving" each morning as he did previously and feels in good health. He has gained 5 kg and has, since 1988, successfully completed the last two years of a degree at The University of British Columbia.

Example 2

Case History - R.R.

R.R., male, 42, underwent surgery for Inflammatory Bowel Disease with partial removal of the colon. After the surgery, he continued to suffer rectal bleeding and ulceration of the mouth. He took aspirin and acetaminophen regularly for pain relief, and underwent surgery for hip replacement. He began taking NAG, 3 g per day, before the hip surgery and continued taking it at that rate during and after the surgery. He reported that the main immediate improvement he experienced was less fatigue and nausea, and a generally better feeling. However, he also noted after several weeks of NAG ingestion that there was a lessening of rectal bleeding, and a decrease in the development of mouth ulcers.

R.R. then underwent surgery for complete removal of the colon. At the time, he stopped taking NAG. He again began to experience difficulties with intestinal discomfort and mouth ulcers. Subsequent to surgery for removal of the colon, he resumed taking NAG at a rate of 3 g per day and found that as before, it made him feel better and lessened the incidence of mouth ulcers.

In the period before colectomy, the evidence of decreased bleeding is of significance and is consistent with the discovery that NAG provides for the formation of essential tissue structures whose deficiency contributes to GI bleeding and oral cavity lesions.

Example 3
Case History - A.B.

A.B., male, 62, was taking aspirin at a rate of 325 mg per day. Gastrointestinal bleeding began suddenly after a time of taking such aspirin. Black stools (which indicate blood from internal bleeding) were accompanied by considerable fresh blood with every movement. Discomfort in the upper abdomen was felt.

A.B. began taking NAG at a dosage of 3-4 g per day, as soon as intestinal bleeding was observed. A.B. also continued to take aspirin. No other medication was taken, such as antacids. Bleeding began to decrease after 3 days of treatment and was completely gone in 4 days. Thirteen days after bleeding had started, A.B. visited a gastroenterologist who advised terminating the aspirin ingestion. The diagnosis was upper GI, probably duodenal bleeding, likely caused or aggravated by the aspirin. Blood tests indicated that haemoglobin fell from 142 to 109 g per litre, representing a loss of about 25% of blood volume. Subsequently, A.B. began to take NAG and after 4 weeks, the upper abdominal discomfort had disappeared

completely. Aspirin consumption was resumed (without the physician's knowledge) but taken together with NAG, A.B. continues to be free of any GI symptoms after 4 months.

As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof. Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.

WHAT IS CLAIMED IS:

1. A method of treating gastrointestinal mucous membrane disorder in the upper gastrointestinal tract of a human being comprising feeding the human being a therapeutic amount of N-acetyl glucosamine on a regular periodic basis.

2. A method according to claim 1 wherein the N-acetyl glucosamine is fed to the human being on a daily basis.

3. A method according to claim 1 wherein the human being is fed about 300 mg to about 10,000 mg of N-acetyl glucosamine per day.

4. A method according to claim 1 wherein the human being is fed about 1,000 mg to about 6,000 mg of N-acetyl glucosamine per day.

5. A method according to claim 1 wherein the human being is fed about 500 mg of N-acetyl glucosamine per day.

6. A method according to claim 3 wherein the N-acetyl glucosamine is incorporated in a pharmaceutically acceptable carrier.

7. A method according to claim 3 wherein the N-acetyl glucosamine is fed to the human being only as required to restore the integrity of mucous membrane tissues in the gastrointestinal tract.

8. A composition useful for treating gastrointestinal mucous membrane disorder in the gastrointestinal tract of a human being comprising N-acetyl glucosamine and a pharmaceutically acceptable carrier.

9. A composition according to claim 8 wherein the N-acetyl glucosamine is present in the amount of about 1,000 mg to about 6,000 mg.

10. A composition according to claim 8 wherein the N-acetyl glucosamine is present in the amount of about 500 mg.

11. A method of inhibiting gastrointestinal mucous membrane disorder in a mammal caused by administration of

pain alleviating agents which comprises feeding the mammal a therapeutic amount of N-acetyl glucosamine in combination with a therapeutic amount of a pain-relieving agent.

12. A method according to claim 11 wherein the pain relieving agent is selected from the group consisting of acetaminophen and acetylsalicylic acid.

13. A method according to claim 11 wherein the pain alleviating agent is acetylsalicylic acid.

14. A method according to claim 11 wherein the pain alleviating agent is acetaminophen.

15. A composition for alleviating pain and inhibiting gastrointestinal mucous membrane disorder in a human being which comprises a mixture of a therapeutic amount of N-acetyl glucoasmine and a therapeutic amount of a pain-alleviating agent.

16. A composition according to claim 15 wherein the pain alleviating agent is selected from the group consisting of acetaminophen and acetylsalicylic acid.

17. A composition according to claim 15 wherein the pain alleviating agent is acetaminophen.

18. A composition according to claim 15 wherein the pain alleviating agent is acetylsalicylic acid.

AMENDED CLAIMS

[received by the International Bureau on 28 September 1993 (28.09.93); new claim 19 added; other claims unchanged (1 page)]

pain alleviating agents which comprises feeding the mammal a therapeutic amount of N-acetyl glucosamine in combination with a therapeutic amount of a pain-relieving agent.

12. A method according to claim 11 wherein the pain relieving agent is selected from the group consisting of acetaminophen and acetylsalicylic acid.

13. A method according to claim 11 wherein the pain alleviating agent is acetylsalicylic acid.

14. A method according to claim 11 wherein the pain alleviating agent is acetaminophen.

15. A composition for alleviating pain and inhibiting gastrointestinal mucous membrane disorder in a human being which comprises a mixture of a therapeutic amount of N-acetyl glucoasmine and a therapeutic amount of a pain-alleviating agent.

16. A composition according to claim 15 wherein the pain alleviating agent is selected from the group consisting of acetaminophen and acetylsalicylic acid.

17. A composition according to claim 15 wherein the pain alleviating agent is acetaminophen.

18. A composition according to claim 15 wherein the pain alleviating agent is acetylsalicylic acid.

19. Use of N-acetyl glucosamine in the manufacture of a pharmaceutical formulation for the treatment of gastrointestinal mucous membrane disorder in the upper gastrointestinal tract of a human being.

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 93/00202

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/70; A61K31/60; A61K31/165

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
P,X	US,A,5 192 750 (BURTON) 9 March 1993 see column 5, line 27 - line 41; claims 1-7; example 3	1-13,15, 16,18
X	EP,A,0 372 730 (THE UNIVERSITY OF BRITISH COLUMBIA) 13 June 1990	1-10
Y	see claims 1-4	14,17
X	EP,A,0 154 523 (K. D. RAINSFORD) 11 September 1985	11,15
Y	see page 2; claims 1,3	14,17

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
19 JULY 1993	03. 08. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FOERSTER W.K.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	BIOCHEMICAL PHARMACOLOGY vol. 29, 1980, pages 1281 - 1289 K.D. RAINSFORD ET AL. 'Biochemical gastroprotection from acute ulceration induced by aspirin and related drugs'	11-13, 15,16,18
Y	see table 2	14,17
A	EP,A,0 234 207 (U. SPECK) 2 September 1987 see the whole document	1-18
A	EP,A,0 013 783 (THE AUSTRALIAN NATIONAL UNIVERSITY) 6 August 1980 see the whole document	1-18
A	EUROPEAN JOURNAL OF PHARMACOLOGY vol. 69, 1980, pages 69 - 77 T. UMBETSU 'Effect of proglumide on glycoprotein synthesis in aspirin-induced gastric erosions in rats' cited in the application see the whole document	1-18
A	US,A,4 748 174 (VERONESI) 31 May 1988 see the whole document	1-18

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

CA 9300202
SA 73912

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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EP-A-0013783	06-08-80	None		
US-A-4748174	31-05-88	DE-A-	3700172	09-07-87
		JP-A-	62252749	04-11-87

EPO FORM P0479